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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,955	11/14/2005	Richard Martyn Angell	P33089	4648

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EXAMINER	
BARKER, MICHAEL P	

ART UNIT	PAPER NUMBER
1626	

NOTIFICATION DATE	DELIVERY MODE
03/04/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

US_cipkop@gsk.com

Office Action Summary	Application No.	Applicant(s)	
	10/522,955	ANGELL ET AL.	
	Examiner	Art Unit	
	MICHAEL P. BARKER	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01/31/2005, Prelim Amd.*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7-11* is/are rejected.

7)☒ Claim(s) *6 and 12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/31/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-12 are pending in this Application.

Information Disclosure Statement

The information disclosure statement filed 01/31/2005 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the *first paragraph* of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8 and **9** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling the compounds of formulae (I) and (II) as p38 inhibitors *in vitro*, does not reasonably provide enablement for 1) A method for treating *any* condition or disease state mediated by p38 kinase activity in a patient, or 2) A method for treating *any* condition or disease state mediated by cytokines produced by the activity of p38 kinase in a patient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Many factors are considered when determining whether the evidence is sufficient to satisfy the enablement requirement and whether any necessary experimentation is "undue." In re Wands, 858 F.2d 731, 742 (Fed. Cir. 1988). These factors include, but are not limited to:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Id. at 738.

Claims 8 and **9** are drawn to methods of treating any and every disease either mediated by p38 kinase activity or mediated by cytokines produced by the activity of p38 kinase activity in a patient, using the compounds of formula (I). The state of the prior art does not support Applicant's claim for the use of small-molecule p38 inhibitors as treatment for any disease mediated by p38 kinase activity or any disease mediated by cytokines produced by p38 kinase activity. There is evidence that p38 pathway kinases may work as anti-inflammatory treatments. Schindler, et al., "p38 Pathway Kinases as Anti-inflammatory Drug Targets", Journal of Dental Research, Vol. 86(9), pp. 800-11 (2007). However, while there are certain selective p38 kinase inhibitors which have good pharmacological activity, most of these compounds demonstrate dose-limiting adverse effects. *Id.* at p. 800. Thus, at least according to Schindler, et al., more research needs to be done in order to determine the clinical efficacy of p38 kinase inhibitors on inflammatory-related diseases.

Applicant provides working examples in the Specification at pp. 126-7. These working examples demonstrate certain of the claimed compounds' ability to inhibit p38 kinase *in vitro*. There is no evidence correlating the *in vitro* data to *in vivo* usage, as claimed in **Claims 8** and **9**.

The state of the prior art, namely pharmacology, involves screening *in vitro* and *in vivo* to determine if the compounds exhibit desired pharmacological activities, which are then tested for their efficacy on human beings. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

There is a lack of evidence in the prior art supporting Applicant's **Claims 8** and **9**. Considering the state of the prior art, in 2007 which is well after Applicant's filing and priority dates, does not yet seem ready to accept p38 kinase inhibitors as capable of treating every disease mediated by protein kinase activity. Alternatively, the amount of experimentation required to enable a PHOSITA to make and use the invention commensurate in scope with **Claims 8** and **9** is undue.

Claim Rejections - 35 USC § 103(a)

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

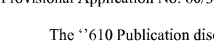
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 1-3, 5, and **7-11** are rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO Publication No. 03/097610 A1, published 05/18/2003, claiming priority to U.S. Provisional Application No. 60/381,092, filed 05/17/2002.

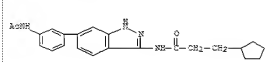
The ''610 Publication discloses several compounds which would anticipate Applicant's Markush language of **Claim 1**, with the exception that Applicant's instant genus must contain a methyl or chloro at the $\mathbf{R^1}$ position. The compounds disclosed in the '610 Publication disclose hydrogen at the equivalent position. Alternatively, Applicant's claimed genus encompasses compounds which simply add a methyl to known compounds.

<u>'610 Publication discloses the following compounds</u>:

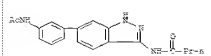
RN 627548-92-6 CAPLUS
CN Benzamide, N-[6-[3-(acetylamino)phenyl]-1H-indazol-3-yl]-3,4,5-trimethoxy- (CA INDEX NAME)



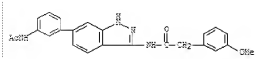
RN 627548-14-0 CAPLUS
CN Cyclopentanepropanamide, N-[6-[3-(acetylamino)phenyl]-1H-indazol-3-yl]- (CA INDEX NAME)



RN 627548-15-1 CAPLUS
CN Butanamide, N-[6-[3-(acetylamino)phenyl]-1H-indazol-3-yl]- (CA INDEX NAME)



RN 627848-91-5 CAPLUS
CN Benzeneacetamide, N-[6-[3-(acetylamino)phenyl]-1H-indazol-3-yl]-3-methoxy- (CA INDEX NAME)



. The '610 Publication discloses a process (pp. 11-19 and pp. 83-86), which can presumably be used to create the aforementioned compounds. The '610 process is similar to Applicant's process of **Claim 10**, in which a compound of formula (II) is reacted with a boronic acid derivative to ultimately yield compounds of formula (I), except the final product of the '610 Publication leads to compounds which vary from Applicant's by a hydrogen-for-methyl.

The level of ordinary skill in pharmacology recognizes compounds which are structurally similar to exhibit similar properties in vivo and in vitro. In fact, the level of skill is high enough, such that numerous courts have recognized that the substitution of a methyl for hydrogen on a known compound is not a patentable modification absent unexpected or unobvious results. *In re Wood*, 199 USPQ 137 (CCPA 1978), *In re Lohr*, 137 USPQ 548 (CCPA 1963); *In re Lincoln*, 126 USPQ 477 (CCPA 1942); *In re Druey*, 138 USPQ 39 (CCPA 1963); *In re Hoehsema*, 158 USPQ 598 (CCPA 1968); and *In re Hoke*, 195 USPQ 148 (CCPA 1977).

The '610 Publication concerns itself with indazoles and aminoindazoles allegedly useful as protein kinase inhibitors. In referencing another WIPO Publication, the '610 Publication notes that certain indazoles and aminoindazoles are known as p38 kinase inhibitors (p. 3). The obviousness of Applicant's method claims, Claims 8 and 9, must be considered in light of the previous enablement rejection. It would not be unobvious for a PHOSITA to simply substitute

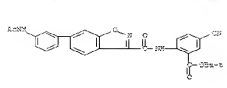
methyl for hydrogen at the **R^1** position to yield compounds which fall squarely within Applicant's claimed genus.

Accordingly, **Claims 1-3**, **5**, and **7-11** cannot be considered patentably distinct over the '610 Publication.

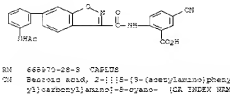
2. **Claims 1-5**, **7**, and **11** are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Publication No. 2004/0110802 A1, published 06/10/2004, claiming priority to U.S. Provisional Application Nos. 60/405,429 and 60/430,592, filed 08/23/2002 and 12/03/2002, respectively. The same rationale as above applies in this rejection, e.g. the '802 Publication discloses compounds which would anticipate Applicant's claimed genus, with the exception that Applicant's instant genus must contain a methyl or chloro at the **R^1** position. The compounds disclosed in the '802 Publication disclose hydrogen at the equivalent position. Alternatively, Applicant's claimed genus encompasses compounds which simply add a methyl to known compounds.

'802 Publication discloses the following compounds:

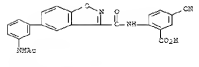
RN 668970-28-0 CAPLUS
CN Benzoic acid, 2-[[[6-[3-(acetylamino)phenyl]-1,2-benzisoxazol-3-yl]carbonyl]amino]-5-cyano-, 1,1-dimethylethyl ester (CA INDEX NAME)



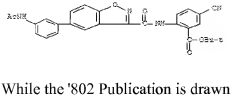
IT 668970-28-8P 668970-26-6P
RL: BCU (Biological study, unclassified); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzoic acid derivs. as antibacterial agents)
RN 668970-26-8 CAPLUS
CN Benzoic acid, 2-[[[6-[3-(acetylamino)phenyl]-1,2-benzisoxazol-3-yl]carbonyl]amino]-5-cyano- (CA INDEX NAME)



RN 668970-28-8 CAPLUS
CN Benzoic acid, 2-[[[6-[3-(acetylamino)phenyl]-1,2-benzisoxazol-3-yl]carbonyl]amino]-5-cyano- (CA INDEX NAME)



IT 668970-19-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; preparation of benzoic acid derivs. as antibacterial agents)
RN 668970-28-6 CAPLUS
CN Benzoic acid, 2-[[[6-[3-(acetylamino)phenyl]-1,2-benzisoxazol-3-yl]carbonyl]amino]-5-cyano-, 1,1-dimethylethyl ester (CA INDEX NAME)



While the '802 Publication is drawn to antibacterials, the nexus between antibacterials and protein kinase inhibitors has been known since at least 1997. Hijikata, et al. "Inhibition of Protein Tyrosine Kinase by 5-S-GAD, a Novel Antibacterial Substance from an Insect", Biochemical and Biophysical Research Communications, Vol. 237, Issue 2, pp. 423-6 (1997).

Claim Rejections - Obviousness Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5 and **7-11** are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over **Claims 1-13**, **15**, **16**, and **18-22** of copending Application No. 10/587,790. This is a provisional double patenting rejection since the conflicting Applications have not yet been patented. **Claims 1-13**, **15**, **16**, and **18-22** of the '790 Application discloses compounds, compositions, a process of preparing the same, and methods of using the same, whose scope is completely encompassed by **Claims 1-5** and **7-11** of the instant Application. Not only is the scope of **Claims 1-13**, **15**, **16**, and **18-22** of the '790

Application encompassed by instant **Claims 1-5** and **7-11**, certain of the species listed in Claim 12 of the '790 Application anticipate the genus of **Claim 1** of the instant Application.

Because of the significant overlap in scope, a PHOSITA would have found the instantly claimed compounds, compositions, process, and methods of use *prima facie* obvious over the '790 Application because the instantly claimed compounds, compositions, and intended uses fall within or parallel the scope delineated by the claims of the '790 Application. The motivation to make the claimed compounds and compositions derives from the expectation that structurally similar or identical compounds and compositions would possess similar activity (i.e. pharmacological use related to p38 inhibition). Although, the conflicting claims are not precisely identical, they are not patentably distinct from each other because Applicant's instantly claimed invention is disclosed within the scope of the co-pending Applications.

According to MPEP 804 I (B)(1), if a provisional obviousness type double patenting rejection is the only outstanding rejection, it may be issued in a junior case, where other terminal disclaimers have been filed in co-pending applications. MPEP 804 I (B)(1) states:

1. Nonstatutory Double Patenting Rejections

If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. If the ODP rejection is the only rejection remaining in the later-filed application, while the earlier-filed application is rejectable on other grounds, a terminal disclaimer must be required in the later-filed application before the rejection can be withdrawn.

Objections

Claims 6, and **12**: Objected to for dependence on rejected base claim.

Claim 6: Certain of the species listed contain Applicant's example numbers, i.e. (GW 824473X)N-Cyclopropyl-4-methyl-3-[1-(methylsulfonyl)-1H-indazol-5-yl]benzamide (GW 825587X) . Please remove all such references from the species of **Claim 6**.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael P. Barker whose telephone number is (571) 272-4341. The examiner can normally be reached on Monday-Friday 8:00 AM- 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Joseph K. McKane, can be reached at (571) 272-0699. The unofficial fax phone for this group are (571) 273-8300.

/Michael P Barker/

Examiner, Art Unit 1626

/Rebecca L Anderson/

Primary Examiner, Art Unit 1626